LIN-28 co-transcriptionally binds primary let-7 to regulate miRNA maturation in Caenorhabditis elegans.

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Public Summary:
Umbilical cord blood-derived haematopoietic stem cells (HSCs) are essential for many life-saving regenerative therapies. However, despite their advantages for transplantation, their clinical use is restricted because HSCs in cord blood are found only in small numbers. Small molecules that enhance haematopoietic stem and progenitor cell (HSPC) expansion in culture have been identified, but in many cases their mechanisms of action or the nature of the pathways they impinge on are poorly understood. A greater understanding of the molecular circuitry that underpins the self-renewal of human HSCs will facilitate the development of targeted strategies that expand HSCs for regenerative therapies. Whereas transcription factor networks have been shown to influence the self-renewal and lineage decisions of human HSCs, the post-transcriptional mechanisms that guide HSC fate have not been closely investigated. Here we show that overexpression of the RNA-binding protein Musashi-2 (MSI2) induces multiple pro-self-renewal phenotypes, including a 17-fold increase in short-term repopulating cells and a net 23-fold ex vivo expansion of long-term repopulating HSCs. By performing a global analysis of MSI2-RNA interactions, we show that MSI2 directly attenuates aryl hydrocarbon receptor (AHR) signalling through post-transcriptional downregulation of canonical AHR pathway components in cord blood HSPCs. Our study gives mechanistic insight into RNA networks controlled by RNA-binding proteins that underlie self-renewal and provides evidence that manipulating such networks ex vivo can enhance the regenerative potential of human HSCs.

Scientific Abstract:
The highly conserved let-7 microRNA (miRNA) regulates developmental pathways across animal phyla. Mis-expression of let-7 causes lethality in C. elegans and has been associated with several human diseases. We show that timing of let-7 expression in developing worms is under complex transcriptional and post-transcriptional control. Expression of let-7 primary transcripts oscillates during each larval stage, but precursor and mature let-7 miRNAs do not accumulate until later in development after LIN-28 protein has diminished. We demonstrate that LIN-28 binds endogenous primary let-7 transcripts co-transcriptionally. We further show that LIN-28 binds endogenous primary let-7 transcripts in the nuclear compartment of human ES cells, suggesting that this LIN-28 activity is conserved across species. We conclude that co-transcriptional interaction of LIN-28 with let-7 primary transcripts blocks Drosha processing and, thus, precocious expression of mature let-7 during early development.